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Review article

Anaphylaxis during anaesthesia: diagnostic approach

Correct management of anaphylaxis during anaesthesia requires a multidisciplinary approach with prompt recognition and treatment of the acute event by the attending anaesthesiologist, and subsequent determination of the responsible agent(s) with strict avoidance of subsequent administration of all incriminated and/or cross-reacting compounds.However, correct identification of the causative compound(s) and safe alternatives is not always straightforward and, too often, not done.This review is not intended to discuss acute management of anaesthesia-related anaphylaxis but summarizes the major causes of anaphylaxis during anaesthesia and the diagnostic approach of this rare but potentially life-threatening complication. Apart from general principles about the diagnostic approach, history taking and importance of tryptase quantification, more specific confirmatory diagnostic procedures are organized on the basis of the major causes of perioperative anaphylactic reactions.

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Anaesthesiologists administer several drugs while providing general anaesthesia. Many of these drugs can elicit adverse drug reactions that fall apart into two major types. First, reactions that are usually dose-dependent and related to the pharmacological properties of the drug and/or its metabolites. Second, reactions that are unrelated to the drug's pharmacological characteristics and that are less dose-dependent. These reactions comprise drug intolerance, idiosyncratic reactions and drug-induced immune-mediated allergic and nonimmune-mediated so-called pseudo-allergic or anaphylactoid reactions. The terms anaphylactic and anaphylactoid, however, have been used inconsistently in the literature. Therefore, the nomenclature task force set up by the European Academy of Allergy and Immunology (EAACI) has proposed that anaphylactic-type reactions should be reclassified into allergic anaphylaxis and nonallergic anaphylaxis. Allergic anaphylaxis being further subdivided in IgE-mediated and non-IgE-mediated reactions (1).

Abbreviations: COX, cyclo-oxygenase; IDT, intradermal test; INN, international nonproprietary name; NMBA, neuromuscular blocking agent; NRL, natural rubber latex; sIgE, specific IgE; SPT, skin prick test.

The exact prevalence of anaphylaxis during anaesthesia is difficult to ascertain. The estimated overall frequency has been reported to vary between 1 in 3500 and 1 in 13 000 procedures in French series (2, 3) and between 1 in 10 000 and 1 in 20 000 in an Australian study (4). The clinical manifestation of these reactions is not infrequently an almost immediate generalized response with bronchospasm and hypotension. The degree of severity varies and does not allow differentiation between an IgE-mediated or non-IgE mediated reaction resulting from nonspecific mediator release (5). The mortality from these reactions is in the range from 3 to 6%, and an additional 2% of patients experience significant residual brain damage (4).

Diagnosis of anaphylaxis during anaesthesia is not always straightforward. It can be hampered as a broad spectrum of different drugs can elicit heterogeneous allergic and nonallergic reactions with distinct and sometimes unclear pathological mechanisms. Problems are certainly compounded as multiple drugs need to be administered during general anaesthesia. In addition, nonanaesthesia related drugs or procedures (e.g. disinfection) are sometimes administered/performed in the perioperative period and can also be the cause of an allergic reaction.

In addition, none of the available diagnostic tests demonstrates absolute accuracy. False-positive test

results may merely cause an inconvenience (unnecessary avoidance of a safe drug), whereas false-negative or equivocal results may be extremely dangerous and severely undermine correct secondary prevention.

The problem in the assessment of the reliability of tests is that, when a single diagnostic test is negative, it is impossible to determine whether it is a false-negative test or whether the patient is tolerant to the tested agent, unless the agent is administered. Ideally, diagnosis of anaphylaxis during anaesthesia should rest upon different confirmatory tests, rather than on a single one. In the event of discrepancies between different tests, an alternative compound that tested completely negative is advocated.

In order to reduce the risk for false-negative results, the diagnostic approach of anaesthetic anaphylaxis is best postponed until 4–6 weeks after the acute event, because of refractoriness of the effector cell or temporarily depletion of specific IgE (sIgE) antibodies (6–9). Alternatively, sensitivity of skin tests might decrease over time, a phenomenon particularly relevant for antibiotics (10, 11). In contrast, skin tests for neuromuscular blocking agent (NMBA) will usually remain positive for a long period of time (12).

In this review, the importance of history taking and tryptase quantification are emphasized. Specific confirmatory diagnostic procedures are organized on the basis of the major causes of perioperative anaphylactic reactions.

Table 1. Differential diagnosis of anaesthesia-related anaphylaxis

Symptoms and sings	Cause
Skin and mucosa: (hives, flush, erythema, urticaria), swelling head and neck	Direct histamine release Venous obstruction Head down position C1-esterase inhibitor deficiency Mastocytosis
Airway comprise, dyspnoea, wheeze, bronchospasm, stridor, difficulty in inflating the lungs	Direct histamine release (e.g. propofol) Acid aspiration Exacerbation of asthma Intubation Oesophageal or bronchial intubation Difficult airway
Fall in blood pressure	Direct histamine release Visceral traction Vasodilatation by drugs (e.g. oxytocin) Cardiac drug effects Concealed hypovolaemia Drug overdose and interactions Gas embolism Hypoxemia Neurocardiogenic syncope Vasovagal reaction Electrolyte disorders

History

To harmonize the diagnostic approach of drug hypersensitivity reactions, members of the European Network for Drug Allergy (ENDA) have developed a specific questionnaire (13). Clinical history should address several major points:

Extent of signs

In most cases, perioperative anaphylaxis is characterized by severe respiratory and cardiovascular manifestations such as arterial hypotension and cardiovascular collapse (2, 3, 5, 14–16). The differential diagnosis of anaesthesia-related anaphylaxis is shown in Table 1.

Drugs and related compounds

Allergy to NMBAs, latex and antibiotics are the most frequent substances involved, allergy to other substances are by far less frequent (Table 2).

Time elapsed between administration and onset-of-symptoms

Clinical signs and symptoms of anaesthetic anaphylaxis usually start within 5–10 min after intravenous administration of the responsible agent but can occur within seconds. In contrast, anaphylaxis from natural rubber latex (NRL) and antiseptics exhibit a more delayed onset and generally occurs during maintenance anaesthesia or recovery, as a result of later application or absorption through skin, mucosal surfaces and/or soft tissues, or removal of a tourniquet (2, 17, 18). In patients allergic to latex, bronchospasm may also be observed early following arrival of a sensitized patient in the operating theatre. Anaphylaxis from colloids can occur immediately or demonstrate a more delayed onset.

Previous allergies from drugs or related compounds

Careful retrospective assessment of medical history and revision of records from local and/or generalized anaesthesia has been demonstrated to reveal symptoms and signs suggestive for the patient being at risk for perioperative anaphylaxis (14–16, 19, 20). For example, in a recent series by Mertes et al. (14) in 30 latex allergic patients (34%), careful revision of medical history performed after the reaction revealed symptoms highly suggestive for latex allergy, already to be present before the reaction. This strongly reinforces the need for an active policy to identify patients at risk during the preanaesthetic visit (9, 20).

Underlying conditions

Identification of particular underlying conditions can also help to identify the causative compound(s). Atopic individuals are particularly at risk for anaphylaxis from NRL during anaesthesia (2, 3, 14–16). Patients with

Table 2. Drugs and related compounds involved in perioperative anaphylaxis (not exhaustive)

Substance	%*	Examples
NMBA	58.2	Succinylcholine
		Benzylisoquinolines: atracurium, cisatracurium, doxacurium, mivacurium
		Aminosteroids: pancuronium, rapacuronium, rocuronium, vecuronium
NRL	16.7	Gloves, tourniquets, catheters
Antibiotics	15.1	β-lactams (penicillins, cephalosporins), vancomycin, quinolones
		Cave: locally applied antibiotics
Colloids	4	Gelatine, hydroxyethyl starch, dextrans, albumins
Hypnotics	3.4	Barbiturates: thiopental, methohexital
		Nonbarbiturates: propofol, midazolam, etomidate, ketamine
Opioids	1.3	Phenanthrenes: morphine, codeine
		Phenylpiperedines: alfentanyl, fentanyl, remifentanyl, sufentanyl and meperidine
Miscellaneous	1.3	Antiseptics: chlorhexidine, povidone iodine
		Iodinated radiological contrast and dyes (patent and isosulphan blue)
		Local anaesthetics: benzoic acid esters and amides
		Aspirin, NSAID and paracetamol (acetaminophen)
		Ethylene oxide
		Protamine and heparins

NMBA, neuromuscular blocking agent; NRL, natural rubber latex; NSAID, nonsteroidal anti-inflammatory drugs.
*According to (14, 49).

mastocytosis are prone to develop perioperative anaphylactic-like reactions and patients with C1-esterase inhibitor deficiency may experience an exacerbation of their disease with cutaneous, laryngeal, or gastrointestinal swellings.

Tryptase

Tryptase is a mast cell tetrameric neutral serine protease that consists out of two major forms, i.e. α and β-tryptase that share approximately 90% of sequence homology. Pro-β-tryptase is secreted constitutively and serves as a measure for mast cell number, whereas mature-β-tryptase rather reflects mast cell activation. Human basophils also contain tryptase, but their levels are 300- to 700-fold lower than in skin or lung mast cells. An elevated total serum tryptase level (pro-β and pro-α and mature-β-tryptase) is therefore highly indicative for mast cell degranulation, as seen in systemic anaphylaxis [for review: (21)].

A rise in total tryptase can be quantified in serum (or plasma) as soon as 30 min after onset of symptoms, but sampling is recommended 60–120 min after onset-of-symptoms (22). Tryptase's half-life is about 120 min, and levels gradually decrease over time. To enable comparison with baseline levels, a new sample should be collected >2 days after the reaction. Tryptase levels may remain elevated in cases of late-onset, biphasic or protracted cell activation (23, 24) and in association with an underlying mastocytosis (25). Discrimination between mature β tryptase and total serum tryptase is not only likely to result in greater specificity in the diagnosis of anaphylaxis but can also be helpful when anaphylaxis occurs in the setting of mastocytosis (26).

'False-negative' results have been attributed to a mechanism where the reaction involves basophils rather than mast cells (22), whereas false positive results have been reported in cases of extreme stress such as hypoxemia and major trauma (27, 28).

Note that serum tryptase does not differentiate between immunological and nonimmunological mast cell activation, and does not contribute in the identification of the causative compound(s). However, in nonimmunological reactions rise of tryptase is less prevalent and usually less pronounced than in immunological mast cell activation (29, 30).

Aetiology

Neuromuscular blocking agents

All NMBA can elicit anaphylaxis and there is an agreement that the short-acting depolarizing succinylcholine poses the greatest risk, despite its close structural homology to acetylcholine (20, 31, 32).

Neuromuscular blocking agents can induce two types of reactions. One is driven by an immunological mechanism and is IgE-dependent with the quaternary ammonium (NH_4^+) structures as main antigenic epitope (33, 34), while the second one, particularly described with benzylisoquinolinium-type NMBA such as mivacurium, atracurium and d-tubocurarine, results from nonspecific stimulation of mast cells (35–37). Cisatracurium, an intermediate acting nondepolarizing stereoisomer of the benzylisoquinolinium agent atracurium and succinylcholine appear to demonstrate the lowest potency of nonspecific mast cell and basophil activation (35, 38, 39).

Controversy has arisen around the potential for an increased prevalence of anaphylaxis to rocuronium.

As summarized by Hepner et al. (40) multiple clinical, methodological and statistical issues might have contributed to this apparent increased potential of anaphylaxis to rocuronium. Comprehensive multi-centric studies are eagerly awaited to elucidate this problem.

Cross-reactivity between NMBA is said to be common because of ubiquitous ammonium groups in these drugs. The estimated prevalence of cross-reactivity between NMBA is about 65% by skin tests and 80% by radioimmuno assay (RIA) inhibition tests. While some pairings are common, the patterns of cross-reactivity vary considerably between patients (14, 16, 41–44). It is unusual that an individual is allergic to all NMBA (41, 44, 45). Cross-reactivity depends on the configuration of the paratope of the antibody, which might either completely correspond to the ammonium epitope or extend to an adjacent part of the NMBA molecule, to the structure of the NMBA (flexibility, inter-ammonium distance) and to the relative affinities of the different NMBA for their sIgE antibodies (34, 45, 46).

Alternatively, it must be kept in mind that some patients might suffer from multiple allergies (3, 14, 16). Consequently, diagnostic approach of anaphylaxis during anaesthesia cannot be considered as complete when it failed to address the possibility of cross-reactivity and/or multi-sensitization, or did not involve identification of safe alternative regimens. This assessment, unfortunately, is fraught with difficulties, as results of skin tests, quantification of sIgE and sIgE inhibition tests do not *per se* reflect the clinical outcome. In the series by Thacker et al. (47), no subsequent reactions were seen if NMBA were avoided in the subsequent anaesthesia, nor were they in patients with severe reactions if the original intradermal test (IDT) had been equivocal or negative. In the patients with a severe reaction and a positive IDT to one or more NMBA, six out of 40 (15%) later anaesthesia using NMBA were associated with clinical problems, three being probable anaphylactic reactions. In a series by Fisher and Bowey (48), one out of 65 patients that had suffered from skin test documented perioperative anaphylaxis suffered from anaphylaxis during subsequent general anaesthesia. Actually, this patient had presented anaphylaxis from pancuronium and reacted subsequently to alcuronium, albeit skin tests for alcuronium, remained negative on two occasions. Therefore, it may, in any case, be safer to avoid NMBA for such a patient in future anaesthesia whenever possible.

Although several issues [skin prick test (SPT) *vs* IDT, maximal concentration to apply, injection volume for IDT, decision threshold, application on forearm *vs* back] remain to be established, for most authors, diagnostic management of anaphylaxis from NMBA rests upon an evocative history corroborated by appropriate skin tests (9, 14, 17, 48, 49). Skin prick test are generally performed on the anterior part of the forearm using a drop of undiluted drug, with the exception of succinylcholine, atracurium and mivacurium. Those compounds need to be tested with a 10-fold up to fivefold dilution in order to avoid nonspecific histamine release (Table 3). For IDT injection of 0.03–0.05 ml of commercially available drugs diluted in physiological solution is performed through a hypodermic needle and reactions are read after 20–30 min by measuring the increase of diameters of wheals and flares. The IDT is considered positive if the diameter of the obtained wheal exceeds 8 mm and doubles with respect to the injection bleb. A serial dilution is advised for IDT starting with a 1/1000 – 1/100 dilution. Injection dilutions are increased progressively as long as results remain negative (Table 3 for maximal concentrations). For a comprehensive comparison between SPT and IDT for NMBA, the reader is referred elsewhere (48). In this study, there was no significant difference in the reliability of diagnostic yield of SPT and IDT. The choice of tests can therefore be based on other factors such as age of the patients (SPT being less painful and thus more suitable for children), cost, and ease of performance. At our departments skin testing starts with SPT and IDT is restricted to patients with negative or equivocal SPT results (Table 4).

Although highly reliable, these skin tests do not demonstrate absolute diagnostic accuracy (50). Disagreement exists also on the specificity of skin tests with NMBA and on the choice of test concentrations defining sensitization. It has been demonstrated that rocuronium and cisatracurium can elicit nonspecific positive IDT in nonallergic individuals at concentrations below those currently applied to diagnose anaphylaxis from those NMBA (51, 52). Moreover, by observing positive SPT for undiluted rocuronium and vecuronium in healthy volunteers, some authors even called into doubt whether NMBA are the principal cause of anaphylaxis during anaesthesia and whether skin tests can be applied to diagnose allergy from NMBA (53). Others, however did not observe false positive SPT for undiluted vecuronium (54) or rocuronium (52). In a prospective study by Tamayo et al. (55), two and zero out of 424 individuals who attended preanaesthesia consultations had a positive SPT for undiluted rocuronium and vecuronium respectively. Eight had a positive SPT for undiluted suxamethonium. An overview of different skin test protocols is provided by Thong et al. (49).

An issue that remains to be addressed is whether there is room for *in vitro* tests. In a series by Fisher et al. (48), reporting several patients with a compelling history of severe perioperative anaphylaxis and negative skin tests, clinical suspicion was corroborated by a RIA. There are currently no NMBA-specific IgE assays readily available, except for suxamethonium (Phadia c202). Unfortunately, on several occasions, sIgE for suxamethonium has been reported to be too insensitive (sensitivity 30–60%) (15, 56, 57). Different authors have proposed to use a quaternary ammonium (choline chloride) (9, 14, 58–60), a p-aminophenylphosphoryl-choline (15, 61), or morphine-based solid phase sIgE (15, 56) assay in preference to different

Table 3. Maximal concentrations for SPT and IDT [adapted from (9)]

Available agents		SPT		IDT		
INN	Conc (mg/ml)	Dilution	Cmax (mg/ml)	Dilution	Cmax (μg/ml)	Comments
Neuromuscular blocking agents						
Atracurium	10	1/10	1	$1/10^3$	10	SPT undiluted (15, 48) IDT $1/10^4$ (224)
Cisatracurium	2	Undiluted	2	$1/10^2$	20	IDT $1/10^3$ (51, 52, 224)
Mivacurium	2	1/10	0.2	$1/10^3$	2	SPT $1/10^2$ (18)
Pancuronium	2	Undiluted	2	1/10	200	IDT $1/10^2$ (224)
Rocuronium	10	Undiluted	10	$1/10^2$	100	IDT $1/10^3$ (18, 52, 224)
Suxa-methonium	50	1/5	10	1/500	100	SPT undiluted (48) IDT $1/10^3$ (225)
Vecuronium	4	Undiluted	4	1/10	400	IDT 1/500 (18, 48) IDT $1/10^3$ (224)
Hypnotics						
Etomidate	2	Undiluted	2	1/10	200	
Midazolam	5	Undiluted	5	1/10	500	IDT $1/10^2$ (48)
Propofol	10	Undiluted	10	1/10	1000	IDT $1/10^2$ (48)
Thiopental	25	Undiluted	25	1/10	2500	IDT $1/10^2$ (48)
Opioids						
Alfentanyl	0.5	Undiluted	0.5	1/10	50	
Fentanyl	0.05	Undiluted	0.05	1/10	5	IDT $1/10^2$ (48)
Meperidine	50	1/2	25	1/20.000	2.5	IDT $1/10^5$ (48)
Morphine	10	1/10	1	$1/10^3$	10	IDT $1/10^5$ (48) SPT 1/40 and IDT $0.5/10^3$ (18)
Remifentanyl	0.05	Undiluted	0.05	1/10	5	SPT 1/20 and IDT 1/200 (18)
Sufentanyl	0.005	Undiluted	0.005	1/10	0.5	
Local anaesthetics						
Bupivacaine	2.5	Undiluted	2.5	1/10	250	
Lidocaine	10	Undiluted	10	1/10	1000	
Mepivacaine	10	Undiluted	10	1/10	1000	
Ropivacaine	2	Undiluted	2	1/10	200	
Antibiotics						
PPL		Undiluted	0.035	Undiluted	35	5×10^{-5} mmol/l
MDM (penicillin)		Undiluted	1	Undiluted	1000	2×10^{-2} mmol/l
Penicillin G		Undiluted	$20–25 \times 10^3$*	Undiluted	$20–25 \times 10^3$*	
Amoxicillin, ampicillin, other penicillins		Undiluted	20–25	Undiluted	$20–25 \times 10^3$	Amoxicillin: 51.7 mmol/l Ampicillin: 54 mmol/l
Cephalosporins		Undiluted	1–2	Undiluted	$1–2 \times 10^3$	
Vancomycin	500	NR	NR	$1/5 \times 10^6$	0.1	IDT ≥10 μg/ml was positive in all controls (98, 99)
Quinolones		Undiluted		$1/10^3$		(102)
Gentamycin	40	Undiluted		$1/10^2$	400	
Miscellaneous						
Chlorhexidine	2%	Undiluted	2%	$1/10^5$	0.0002%	
Protamine	50	Undiluted	50	$1/10^3$	50	
Oxytocin		1/10	1*	$1/10^2$	0.1*	
Hydroxyethyl starch		Undiluted		$1/10^2$		
Gelatine	±35	Undiluted		Undiluted		(226)
Dextran 40/70	6–10	Undiluted	6–10	$1/10^2$	600–1000	
Aprotinin	10^4	Undiluted	10^4*	$1/10^2$	10^2*	

SPT, skin prick tests; IDT, intradermal tests; INN, international nonproprietary name; Cmax, maximal concentration; PPL, benzylpenicilloyl poly-L-lysine; MDM, minor determinants mixture; NR, not relevant.

SPT are considered positive when the wheal and flare reaction exceeds 3/3 mm. IDT are performed by injecting 0.05 ml into the dermis of the forearm or back through a hypodermic needle. Reactions are read after 20 min. The IDT is considered positive if the diameter of the obtained wheal exceeds 8 mm and doubles with respect to the injection bleb.

*For penicillin G, oxytocin and aprotinin concentrations are expressed in IU/ml (not mg/ml).

NMBA-specific IgE assays to assess sensitization from quaternary ammonium determinants of NMBA. In several of these studies, the assays proved to be highly efficient with sensitivity and specificity approximating or exceeding 90%. However, Florvaag et al. (57) recently called into question the practice to adopt a morphine-

Table 4. Diagnostic procedures organized on the bases of most important causes [adapted from (227)]

	NMBA	NRL	Antibiotics	Colloids	Hypnotics	Chlorhexidine	LA
History	S	S	S	S	S	S	S
SIgE	Suxamethonium Morphine Rocuronium	S	Penicilloyl G Penicilloyl V Amoxycilloyl Ampicilloyl Cefaclor	Gelatine	Thiopental	S	NA
SPT	S1	S	S1*	S1	S1	S1	S1
IDT	S1	NR	S1*	S1	S1	S1	S1
SCT	NR	NR	NR	NR	NR	NR	S1
BAT	S	A	A	S	A	A	NR
CPT	NR	A	NR	NR	NR	NR	S2
IVPT	S3	NR	S3	NR	S3	NR	NR

NMBA, neuromuscular blocking agent; NRL, natural rubber latex; LA, local anaesthetic; sIgE, specific IgE; SPT, skin prick test; IDT, intradermal test; SCT, subcutaneous test; BAT, basophil activation test; CPT, cutaneous provocation test; IVPT, intravenous provocation test.
S, standard; NA, not available; NR, not relevant; A, alternative when there is a discrepancy between clinical suspicion and IgE and/or SPT.
S1: serial testing with suspected drug starting with SPT. Subsequently IDT and/or SCT, when relevant and only when SPT remains negative or equivocal.
S2: with alternative local anaesthetic that tested negative in SPT and IDT.
S3: with alternative drug that tested negative in SPT, IDT and BAT and when anaesthesia is planned.
Maximum concentrations for SPT and IDT are summarized in Table 3.
*Skin tests include benzylpenicilloyl poly-l-lysine and minor determinants mixture.

based assay to diagnose anaphylaxis from NMBA, as they demonstrated morphine sIgE to be common in Norwegian healthy blood donors and a general 'allergic' population. It was demonstrated that the availability of pholcodine-containing cough syrups was the most likely explanation for this sensitization.

Although quantification of sIgE and sIgE inhibition experiments have been applied to assess cross-reactivity between different NMBA (43), prudence should be called upon the interpretation of the results. Quantification of sIgE and sIgE inhibition tests might simply reflect *in vitro* cross-reactivity without any clinical relevance (45, 56, 62). Cross-reactivity and identification of a safe alternative should primarily be asserted by skin tests, but functional assays such as histamine release tests (45) or flow-assisted analysis of *in vitro* activated basophils (63) can provide valuable adjuncts.

Evidence has accumulated that flow cytometric analysis and quantification of *in vitro* activated basophils can add to the diagnosis of anaphylaxis from NMBA (64–67). In these series, sensitivity and specificity of the technique is around 60 and 90% respectively. In an own study, sensitivity of the basophil activation assay for rocuronium was 92%, whereas specificity was 100% (63). In addition, the technique proved clearly complementary to skin tests in the assessment of cross-reactivity and identification of a safe alternative. Larger comprehensive studies are required to confirm these data and allow the technique to enter mainstream diagnostic approach.

A systematic preoperative screening for the potential of anaphylaxis from NMBA is not recommended (20, 33, 68).

Natural rubber latex

IgE-mediated NRL allergy has become a well-defined condition with recognized risk groups, established diagnostic tools, and adequate prevention strategies (69, 70). In 1984, Turjanmaa et al. (71) described the first cases of NRL-associated intra-operative anaphylaxis. By 1996, NRL was reported to account for approximately 20% of anaesthetic anaphylaxis, and, by 2000, had been reported to account for as much as 17% of these reactions in the general population (14) and 27–76% in a paediatric population (2, 16). However, longitudinal epidemiological data suggest anaesthetic anaphylaxis from NRL might be 'over the top' (14), in part because of an increased awareness and primary preventive measures. In a recent Norwegian series, NRL accounts for only 3.6% of the cases of perioperative anaphylaxis (15), probably reflecting the large use of a latex free environment and the use of unpowdered gloves.

The at-risk individuals for perioperative anaphylaxis from NRL can be subdivided into those genetically predisposed (i.e. atopics) and those with significant exposure such as healthcare workers and children requiring multiple or repetitive surgical and medical interventions (e.g. neural tube defects, spinal cord trauma, urogenital malformations) that need chronic bladder care with repeated insertion of NRL catheters or chronic indwelling catheters.

In contrast, adult patients with spinal cord injury and repeated latex exposure seem not at risk for latex allergy (72).

Natural rubber latex allergy is associated with serological and/or clinical cross-reactivity for numerous plant allergens and in 1994 a 'latex-fruit syndrome' has been postulated (73). The foods most frequently involved are banana, chestnut and avocado. Although NRL allergy precedes food hypersensitivity in most patients, the opposite has been observed in some patients (14, 73, 74).

A questionnaire is not sufficiently reliable to diagnose NRL allergy (75, 76). In most patients, diagnosis of NRL anaphylaxis can readily be established by quantification of sIgE (k82), skin tests, or both (77–79). Although these tests are highly reliable, results of are not always unequivocal (80), and some patients might need additional tests such as basophil activation (81–83) or challenge tests (84, 85) to establish diagnosis.

Antibiotics

Penicillins and other β-lactams such as cephalosporins elicit adverse drug reactions mediated by specific but heterogeneous and frequently unknown mechanisms. However, from clinical and immunological studies it

emerges most of the immediate perioperative reactions to be IgE-mediated. Taken together, penicillins and cephalosporins elicit approximately 70% of perioperative anaphylactic reactions elicited by antibiotics (3, 14).

The diagnostic approach for allergic reactions to (β-lactam antibiotics have recently been standardized under the aegis of ENDA, the EAACI interest group on drug hypersensitivity (86). In this position paper two slightly different algorithms that combine skin tests, quantification of sIgE, and in selected cases drug provocation tests are described. Skin tests start with SPT, which are, if negative, followed by IDT. Skin testing should not be limited to the classical and commercial reagents benzylpenicilloyl poly-L-lysine (PPL) and so-called minor determinants mixture (MDM), but should include amoxicillin (AX) and ampicillin (AMP), as well as the culprit compound(s) (87, 88)). Maximum concentrations for SPT and IDT for PPL, MDM, AX, AMP and other penicillins and for most cephalosporins are summarized in Table 3. A kit with major and minor determinants is provided by Diater Laboratories (Madrid, Spain) but needs additional validation (89).

In vitro assays to quantify sIgE for several penicillin determinants (Phadia penicilloyl G (c1), penicilloyl V (c2), amoxycilloyl (c6), ampicilloyl (c5) and cefaclor (c7)) are available and, although generally less sensitive than skin tests, constitute a valuable and safe tool in the diagnostic approach for patients with suspected IgE-mediated β-lactam allergy (90–93).

In a comparison between quantification of sIgE and basophilic CD63 expression, in 58 patients suffering from skin test-proven β-lactam allergy and 30 healthy control individuals, sensitivity and specificity of the assays approximated 38% and 87% for sIgE and 50% and 94% for the basophil activation test respectively (90). Similar results were observed in the study by Torres et al. (94). Provocation tests with β-lactam antibiotics should be restricted to those patients with a suggestive history and negative IgE and skin test investigations (86).

Vancomycin can elicit two types of immediate hypersensitivity reactions; the red man syndrome and anaphylaxis (95–100). The red man syndrome typically consists of pruritus, burning sensation, an erythematous eruption that spreads over face, neck and upper torso. Less frequently angio-oedema, dyspnoea and hypotension can occur. Signs generally appear within 5–10 min after start of infusion and are often associated with too rapid (<1 h) infusion of the first dose and result from nonspecific mediator release from mast cells and basophils. Teicoplanin can also cause red man syndrome (96, 101). Documented cases of IgE-mediated allergy from vancomycin remain anecdotal (95, 99). Original intradermal test with vancomycin should be performed below a concentration of 10 μg/ml (98, 99).

Quinolones constitute the third most important group of antibiotics involved in perioperative anaphylaxis (14). Unlike penicillin, there are no validated skin testing reagents and readily available sIgE assays to aid in confirming the presence of sIgE antibodies to vancomycin and quinolones (102, 103). Manfredi et al. (102) have shown that about 50% of patients with quinolones induced anaphylaxis have IgE antibodies, and frequently demonstrate cross-reactivity. Skin tests with quinolones are not reliable, as these drugs can induce direct histamine release (104, 105).

For a summary about hypersensitivity reactions to other non-β-lactam antibiotics, the reader is referred to the review by Tilles and Slatore (106).

It should also be emphasized that antibiotics such as bacitracin and rifamycin, applied locally to irrigate wounds, can also elicit potentially life-threatening anaphylaxis and must not be overlooked (3, 19, 107–109). Anaphylactic reactions from locally applied antibiotics have been reported after removal of tourniquet (19).

Hypnotics

Allergy from thiopental, a short-acting barbiturate anaesthetic, was first reported during World War II (110). Older estimates of reaction prevalence range from 1 in 30 000 (111) up to 1 in 400 (112), but in more recent surveys anaphylaxis from thiopental sodium is only rarely or even not observed, probably as a result from less intensive application (3, 14–16, 18). Diagnosis of anaphylaxis from thiopental generally rests upon skin tests and/or quantification of sIgE that is available for research purposes. As for most other hypnotics SPT are performed with undiluted drug, whereas for IDT 0.05 ml of a 10- to 100-fold dilution of the commercially stock solution is tested (Table 3). Thiopental sodium may show cross-reactivity with barbiturate analogues such as pentobarbitone, phenobarbitone, barbitone and methohexital (113).

Methohexital is a barbiturate derivative generally applied for brief surgical procedures and rarely induces anaphylaxis. Although their frequent application, anaphylaxis from nonbarbiturate hypnotics is rare (3, 14–16, 18).

Propofol (2-6 diisopropylphenol) is an alkyl phenol that bears two isopropyl groups that may act as antigenic epitopes (114). There is one report on allergy from propofol that emphasis the drug should be omitted in patients with allergy from eggs or soy, from which lecithins are present in the propofol vehicle (115). However, up to now we did not observe anaphylaxis from propofol in patients with egg or soy allergy. According to sIgE data, it has been postulated that propofol is contra-indicated in patients with anaphylaxis from NMBA (114). This is, however, not the experience of others (20). Actually, in analogy with allergy for thiopental sodium, patients with propofol allergy can demonstrate clinically irrelevant IgE antibodies against NMBA. Diagnosis of propofol allergy has been established by skin tests, sIgE and histamine-release tests (114). Alternatively, propofol has been demonstrated to induce a concentration-dependent histamine release from human

lung mast cells (116) and can elicit bronchospasm at higher doses.

Anaphylaxis from etomidate, an imidazole derivative, that is structurally unrelated to any of the other intravenous hypnotics and ketamine, a phenylcyclidine derivative, is extremely rare (14, 16).

Midazolam hydrochloride is a short-acting imidazobenzodiazepine that rarely causes anaphylaxis (3, 14). In those series, diagnosis of midazolam anaphylaxis was established upon SPT with undiluted drug and IDT.

Opioids

Generalized reactions to opioids [e.g. morphine, codeine and synthetic opioids such as meperidine (international nonproprietary name, INN: pethidine)] usually result from nonspecific mast cell activation, rather than from IgE-mediated degranulation (117, 118). Particularly, skin mast cells are sensitive to nonspecific activation by opioids. In contrast, mast cells of the heart, lung and gastrointestinal system as well as basophils are not sensitive to opioids (116, 119, 120). As a consequence, most of these reactions are not life-threatening and include pruritus, urticaria and mild hypotension but are frequently misinterpreted as drug allergy. Fentanyl appears not to induce nonspecific mediator release from mast cells (116–119).

Evidence for IgE-mediated reactions from opioids in the literature is restricted to some case reports on anaphylaxis from fentanyl, meperidine, papaveratum, codeine, morphine and pholcodine (121–126). None of these cases reports on potential cross-reactivity between the different opioid subclasses phenanthrenes (e.g. morphine, codeine), phenylpiperedines (alfentanyl, fentanyl, remifentanyl, sufentanyl and meperidine) and diphenylheptanes (methadone and propoxyphene). Therefore, historically, the recommendation has been to switch to a different subclass with a distinct chemical structure in order to avoid antibody recognition (127). However, the observation that codeine, meperidine and methadone, representatives of the different opioid subclasses react with morphine antibodies put into question this practice (87, 123). In the absence of validated drug specific diagnostic tools, correct diagnosis of opiate allergy remains a clinical challenge. Particularly, because SPT have been demonstrated to be not useful for this purpose (118, 128) and morphine sIgE, as addressed above, does not *per se* indicate sensitization from this drug, but might rather mirror sensitization from quaternary ammonium structures from NMBA. Placebo-controlled challenges may be required to diagnose opioid allergy (118, 128).

Aspirin and other nonsteroidal anti-inflammatory drugs

For a review on hypersensitivity from Aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAID), the reader is referred elsewhere (129, 130). During the last two decades, evidence has emerged that bronchospasms and urticaria/angio-oedema from these drugs result from inhibition of cyclo-oxygenase (COX)-1 iso-enzyme with subsequent depletion of prostaglandin E2 and unrestrained synthesis of cysteinyl leukotrienes (cys-LT) and release of mediators from mast cells and eosinophils (131). Weak COX-1 inhibitors, such as paracetamol and partial inhibitors of both COX-1 and COX-2, such as nimesulide and meloxicam, can cross-react but generally only at high drug doses. Selective COX-2 inhibitors do rarely precipitate asthma and/or urticaria/angio-oedema and are generally (but not always) well tolerated (132).

Alternatively, all NSAIDs, including the selective COX-2 inhibitors, can induce urticaria or anaphylaxis (133).

Currently, diagnosis of ASA and NSAID-induced hypersensitivity reactions can only be established by drug provocation tests (131, 134). There are currently no sIgE assays for ASA or NSAID available. The diagnostic value of histamine and cys-LT release assays (135–137) and flow-assisted quantification of *in vitro* activated basophils (138, 139) remains to be established. In our department patients with hypersensitivity reactions from ASA and NSAID are challenged with incremental doses of a selective COX-2 inhibitor, and some positive provocations have been observed.

Acetaminophen (international INN: paracetamol) is an extensively used analgesic and antipyretic that was perioperatively frequently administered intravenously as propacetamol (*N*,*N*-diethyl glycidyl ester). Propacetamol has been withdrawn from the market and intravenous paracetamol is now available. Hypersensitivity to acetaminophen seems to be rare (140, 141) and evidence for an IgE-mediated mechanism is anecdotal (142, 143).

Plasma volume expanders (colloids)

Today, colloids have been recognized to cause up to 4% of all perioperative anaphylactic reactions (3, 14, 15). These reactions were severe in 20% of the cases and generally occurred 20 min after start of infusion. Fatalities to colloids have been reported (144). For a comprehensive review of 'anaphylactoid' reactions to colloids, the reader is referred elsewhere (145). Although the mechanisms of these reactions remain poorly understood, evidence has emerged for an IgE-mediated mechanism in some patients.

Anaphylaxis to gelatine in condiments (146, 147) and, at least in some countries, vaccines has been increasingly recognized (148–150). It seems obvious to avoid gelatine-based colloids in patients with known gelatine allergy (147). Diagnosis from IgE-mediated gelatine allergy is generally established upon quantification of sIgE (Phadia c74) (151), appropriate skin tests (48, 148, 152, 153) or basophil activation assays such as histamine release tests

(152, 154) and flow assisted quantification of *in vitro* activated basophils (154).

Hydroxyethyl starch (HES) compounds are synthetic polymers derived from amylopectin, and are classified according to their *in vitro* molecular weight in high, medium and low molecular weight preparations. However, HES is metabolized, and both the pharmacodynamic properties and adverse events depend on the *in vivo* molecular weight (155–157). Hetastarch and pentastarch have a molecular weight of 480 kDa and 250 kDa respectively. In the absence of sIgE assays, diagnosis of anaphylaxis from HES generally relies upon skin tests (18, 145). Our group was the first to provide an evidence for an IgE-mediated reaction towards pentastarch using passive donor basophil sensitization experiment (158). The clinical relevance of IgG, IgM and IgA antibodies against HES remains unknown (159).

High-molecular-weight dextrans (40, 70 and 75 kDa) are accompanied by significant side effects including dextran-induced allergic reactions (DIAR) (145, 160). These are immune complex mediated by dextran-reactive antibodies of the IgG class. Severe DIAR is characterized by bronchospasm, profound hypotension, cardio-respiratory arrest and fatalities. In order to avoid this potentially life-threatening complication associated with dextran, the DIAR, hapten dextran (1 kDa) is infused before starting the first application of dextran (161, 162). Nevertheless, accidents still happen (163, 164). Given the mechanism of DIAR, the diagnostic value of skin tests is not established. Dextran reactive antibodies can be quantified, but the technique is not readily available.

Anaphylaxis from albumin is anecdotal (145, 151, 165). Egg allergy does not seem a contraindication to the administration of albumin (166).

Chlorhexidine and other antiseptics

Chlorhexidine, a cationic bisguanide antiseptic and disinfectant, is active against a broad spectrum of bacteria, mycobacteria, some viruses, and some fungi. Chlorhexidine salts can trigger irritant dermatitis, allergic contact dermatitis, urticaria/anaphylaxis and combined urticaria/anaphylaxis and allergic contact dermatitis [for review: (167)]. In some patients, anaphylaxis to chlorhexidine, was preceded, sometimes by years, by chlorhexidine-induced contact dermatitis (168). Evidence for an IgE-mediated hypersensitivity to chlorhexidine was first provided in 1984 (169) and hapten inhibition studies have shown the entire chlorhexidine molecule to be complementary to the IgE antibody binding sites and the 4-chlorophenol, bisguanide and hexamethylene structures together constitute the allergenic determinant (87, 170). Symptoms of chlorhexidine anaphylaxis have been attributed to cutaneous, percutaneous, mucosal, and parenteral application. Life-threatening reactions with profound hypotension, ventricular fibrillation and cardiac ischaemia are generally associated with mucosal or parenteral exposure as might occur during application of urethral gels, implanted antimicrobial surgical mesh, and insertion of chlorhexidine-coated central venous catheters respectively. Severe, potentially life-threatening anaphylaxis from simple cutaneous application such as perioperative skin disinfection and wound cleansing remains anecdotal and probably underestimated. In a recent survey, chlorhexidine accounted for 27% of the overlooked perioperative hypersensitivity reactions (171). Note that this prevalence of chlorhexidine anaphylaxis is not observed in other countries. Part of the problem could be related to the concentration of chlorhexidine in antiseptics used in different countries.

Up to now, most authors have relied upon skin testing to confirm clinical suspicion of anaphylaxis from chlorhexidine (17, 167). In an own series, diagnosis of anaphylaxis from chlorhexidine was readily established with SPT applying a 10-fold dilution of the available stock solution of chlorhexidine digluconate (2%) in alcohol (70%). In contrast, control individuals demonstrated negative SPT responses with the undiluted antiseptic (172). In this paper, it is also demonstrated quantification of chlorhexidine-specific IgE and flow cytometry assisted quantification of *in vitro* activated basophils to constitute reliable instruments to document anaphylaxis from chlorhexidine. The sIgE assay for chlorhexidine has now become commercially available (c8, Phadia).

Although povidone-iodine (betadine) is a commonly applied topical antiseptic solution, anaphylaxis to this compound is rare (14, 19, 30, 59, 173–177). Clinical suspicion of povidone-iodine anaphylaxis was generally corroborated by skin test and basophil activation assays.

Local anaesthetics

Local anaesthetics (benzoic acid esters or amide derivatives) are commonly used during general anaesthesia but their application is often not obvious and/or unmentioned in the anaesthetic reports, e.g. when applied to alleviate propofol-induced vascular pain.

Although generally considered as intrinsically safer than general anaesthesia, local anaesthetics can elicit a variety of side effects (178–180). Immunological reactions to local anaesthetics, particular the newer amides, however, remain anecdotal and symptoms usually result from vasovagal episodes or anxiety reactions (178, 181–183). Acute disorientation or seizures may occur after overdosage or inadvertent intravenous injection. In addition, many local anaesthetics contain adrenaline as a vasoconstricting agent (184). Local anaesthetics can also produce sympathetic effects that may include tremulousness, palpitations, tachycardia, diaphoresis, light-headedness, or near syncope, irrespective the presence or absence of vasoconstricting agents. Other excipients associated with local anaesthetics such

as anti-oxidants and preservatives (bisulphites, parabens, carboxymethylcellulose, para-aminobenzoic acid) can also elicit adverse and even allergic reactions (184–188).

Challenge tests remain the gold standard, or rather reference test to diagnose anaphylaxis from local anaesthetics and different protocols exist (49, 180, 189, 190).

Protamine and heparins

Protamine is a low molecular weight protein (4.5 kDa) isolated from the sperm of various fish species. When administered alone, protamine has an anticoagulant effect. However, when it is given in the presence of heparin, a stable salt is formed which results in the loss of anticoagulant activity of both drugs. Protamine can cause significant histamine release resulting in (fatal) hypotension and bronchospasm, and also causes pulmonary hypertension (191–193). In a prospective study in 243 patients who underwent cardiopulmonary bypass surgery, Weiler et al. (194) reported an immediate adverse reaction towards protamine in 26 of the patients, 1.6% had a drop in blood pressure immediately after administration of the drug. Previous exposure to protamine through use of protamine-containing insulins (NPH: neutral protamine Hagedorn) or during heparin neutralization, vasectomy and fish allergy have been proposed to predispose to the development of untoward reactions from the subsequent use of this drug (191, 194, 195). However, these findings could not be confirmed (196, 197). Although skin tests with protamine may be helpful in identifying a possible IgE-mediated response in selected cases, these tests must be interpreted with caution because they do not necessarily predict clinical sensitivity and do not identify all patients at risk (198). A sIgE protamine is available (rc207).

In rare occasions, heparins have been identified as the cause of anaesthetic anaphylaxis (199). The immediate and delayed allergic adverse events of unfractionated and low molecular weight heparins, as well as the diagnostic management, have recently been summarized elsewhere (200).

Aprotinin

Aprotinin is a naturally occurring polybasic serine protease inhibitor, purified from cattle lung. It is the only agent with class A level 1 evidence for reduction transfusion rates and return to operating theatre to control bleeding after heart surgery. Principal on the list of safety issues raised over the years are increased risk for thrombosis and renal dysfunction (201). With multiple administrations, hypersensitivity reactions have emerged as a further major safety concern (202). The risk of anaphylaxis is approximately 2.8% in re-exposed patients. From 1963 to 2003, 124 cases of aprotinin-induced anaphylaxis were reported in 61 publications. Eleven patients died. The re-exposure interval was < 3 months in 72% (38 of 53 patients) (203). However, anaphylaxis upon first exposure as been described (203, 204). Anaphylaxis from aprotinin can result from intravenous administration as well as topical exposure (e.g. fibrin sealants) (205).

Skin tests and quantification of sIgE and sIgG antibodies for aprotinin have a good negative predictive value but positive predictive value is poor (202–204).

Hyaluronidase

Hyaluronidase is a proteolytic enzyme that is sometimes used as a spreading factor in order to improve diffusion of other drugs. Typical applications are as an adjunct to local anaesthesia, especially in nerve blocks and ophthalmic anaesthesia. Hypersensitivity reactions towards hyaluronidase comprise local acute or delayed reactions as well as more generalized anaphylactic reactions. Diagnosis of IgE-mediated allergy to hyaluronidase can be confirmed by skin tests, quantification of sIgE or flow cytometry (206).

Oxytocin

Oxytocin is a synthetically manufactured hormone that stimulates contractions of uterine smooth muscle and is indicated for induction and augmentation of labour as well as in abortions. Anaphylaxis from oxytocin is rare (15, 207, 208) and diagnosis is generally based upon skin tests. Note that oxytocin can produce hypotension through a pharmacodynamical mechanism when given in larger intravenous boluses, an interesting differential diagnosis that could be mentioned (209).

Dyes

Patent blue (alphazurine 2G) is an aniline dye with ubiquitous application in textile and paper industry, agriculture, cosmetics and medical settings. Besides its former application as antibacterial and antifungal agent, it has long been used for lymphography. Today, it is the dye of choice for intra-operative sentinel lymph node mapping for breast cancer and melanoma. Hypersensitivity reactions towards patent blue have been reported since 1966 (210). Most patients have suffered from reactions during lymphography. Anaphylaxis can also result from alternative routes of administration (211–213).

The second dye applied for sentinel node mapping is isosulphan blue (Lymphazurin), a derivative from patent blue. Anaphylaxis from isosulphan blue was first described in 1985 (214). Since several case reports of anaphylaxis from this dye have been published (215–218). Because of the extensive cross-reactivity between isosulphan blue and patent blue, the dyes cannot be considered as reciprocal alternatives (212, 218).

Anaphylaxis due to other blue dyes such as indigo carmine (sodium indigotindisulfonate) (219, 220) and methylene blue (221, 222) seems anecdotal. Because methylene blue has been shown to be equally effective for mapping of sentinel lymph nodes and appears not to pose an important risk for anaphylaxis, it was proposed as the dye of choice for mapping studies (223). Skin tests and basophil activation tests constitute confirmatory procedures for anaphylaxis from blue dyes and can contribute to the identification of potential cross-reactive and safe alternative dyes (213, 218, 222).

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